A New Efficient Synthesis of Spirocyclic Benzopyrans

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Abstract: Starting from a protected β-amino ketone and several 3-chromanones, spirocyclic benzopyran derivatives were obtained via a Mannich type condensation.

Key words: spiro compounds, heterocycles, protecting groups, ketones, chromanones, Mannich bases, condensation

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter of the CNS, which is involved in a lot of physiological and pathophysiological processes in the brain. Dysfunction in serotoninergic systems has been related to various behavioral problems (eg memory, sleep) but also to some neuropsychiatric disorders such as anxiety, schizophrenia or Alzheimer’s disease. All these processes are mediated by the specific interaction of 5-HT with several different serotoninergic receptors which have been listed in seven main types (5-HT1–5HT7). Refinement of relationships between the receptor structure and the physiological answer led to some subdivisions, such as 5-HT1A which includes six subtypes (5-HT1A–5HT1F). Synthesis of 5-HT1A agonists appear to be very attractive, due to their role in the treatment of anxiety and depression behavioral disorders. Previous work from our laboratory has led to new potential therapeutic agents which demonstrated a good affinity and a high selectivity for the 5-HT1A and 5-HT3 receptors. Among them, compound S22178 has showed high affinity towards 5-HT1A receptors at nanomolar scale (8.8 nM) (Figure 1).

Figure 1

Precedent synthesis of this compound, in racemic form, was realized in ten steps, starting from 2,6-dimethoxybenzaldehyde, in an 11% overall yield. In order to improve the final yield for biological tests and to offer an easy and general access to substituted derivatives, a new synthesis of the 3’,4’-dihydrospiro[piperidine-2,5’(2H)-benzopyran] framework was needed.

We have previously described that 2-spiropiperidines could be easily obtained from cyclic ketones and protected β-amino ketone through an intramolecular Mannich type reaction as the key step (Scheme 1).

Scheme 1

Following this methodology, spirocyclic aminochromans could be prepared from 3-chromanones and compound as described in Scheme 2.

Scheme 2

Since amino ketone is simply obtained from methyl vinyl ketone, according to Raphaël’s procedure, an efficient synthesis of 3-chromanone skeletons was required. For this purpose, we used a general and efficient procedure. So, condensation of salicylaldehyde or substituted derivatives with acrylonitrile, in the presence of DABCO gave 3-cyano derivatives in moderate to good yields (Scheme 3, Table 1). Further treatment with dilute NaOH, followed by acidification furnished corresponding carboxylic acids. A modified Curtius reaction was then realized using diphenylphosphoryl azide (DPPA) followed by acidic hydrolysis, and led to 3-chromanone framework compounds, except for 12f.
which gave a complex mixture in which no desired derivative 8f was detected.

Scheme 3

Thus, compound 8a and amine 1 were involved in the cyclization step, following our protocol used for cyclanones11 (TsOH, then BF₃·Et₂O, CH₂Cl₂, reflux) (Scheme 4).

Scheme 4

Table 1 Synthesis of Nitriles 11, Acids 12 and Chromanones 8

<table>
<thead>
<tr>
<th>Compounds (yields, %)</th>
<th>11</th>
<th>12</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>11a (80)</td>
<td>12a (96)</td>
<td>8a (66)</td>
</tr>
<tr>
<td>5-OMe</td>
<td>11b (65)</td>
<td>12b (99)</td>
<td>8b (72)</td>
</tr>
<tr>
<td>6-OMe</td>
<td>11c (77)</td>
<td>12c (86)</td>
<td>8c (43)</td>
</tr>
<tr>
<td>7-OMe</td>
<td>11d (65)</td>
<td>12d (100)</td>
<td>8d (57)</td>
</tr>
<tr>
<td>8-OMe</td>
<td>11e (72)</td>
<td>12e (95)</td>
<td>8e (60)</td>
</tr>
<tr>
<td>5-NO₂</td>
<td>11f (48)</td>
<td>12f (58)</td>
<td>8f (0)</td>
</tr>
<tr>
<td>5-CF₃</td>
<td>11g (55)</td>
<td>12g (87)</td>
<td>8g (67)</td>
</tr>
<tr>
<td>5,6-(C₆H₄)</td>
<td>11h (57)</td>
<td>12h (99)</td>
<td>8h (56)</td>
</tr>
</tbody>
</table>

Table 2 Synthesis of Spirocyclic Derivative 9a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i) MgSO₄, TsOH, CH₂Cl₂, reflux, 2 h; ii) Ti(i-i-PrO)₄, CH₂Cl₂, reflux</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>i) MgSO₄, TsOH, CH₂Cl₂, reflux, 2 h; ii) TiCl₄, CH₂Cl₂, reflux</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>i) MgSO₄, TsOH, CH₂Cl₂, reflux, 2 h; ii) TMOTf, CH₂Cl₂, reflux, 18 h</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>i) MgSO₄, TsOH, CH₂Cl₂, reflux, 18 h; ii) BF₃·Et₂O, CH₂Cl₂, reflux, 18 h</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>i) MgSO₄, TsOH, CH₂Cl₂, reflux, 8 h; ii) BF₃·Et₂O, CH₂Cl₂, reflux, 18 h</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>i) MgSO₄, TsOH, CH₂Cl₂, reflux, 2 h; ii) BF₃·Et₂O, CH₂Cl₂, reflux, 18 h</td>
<td>52</td>
</tr>
</tbody>
</table>

Entry 6 summarizes the best conditions found, which furnished 9a in a 52% overall yield. Formation of the desired product was not observed after prolonged reaction time (entries 4 and 5) due probably to decomposition of the transient imine. Comparison of Lewis acids (entries 1, 2, 3 and 6) showed that BF₃·Et₂O is a suitable catalyst for this reaction. A detailed explanation is actually unavailable, but this trend could be the result of a better activation of the acetal opening.

With these conditions in hand, we reacted compounds 8b–h with amine 1. Results of these reactions are given in Table 3.

Substituted spirocyclic aminochromans 9 were obtained in approximately 32 to 45% yields, except for 8b and 8e which gave exclusively pyrido[2,3-c]chromans 13 and 14. Formation of these compounds could be rationalized through the mechanism depicted in Scheme 5.

The initially formed imine was in equilibrium with the enamine form, which reacted immediately with the Lewis activated oxygen. The equilibrium between iminium and enamine, followed by elimination of glycol led to the dihydro pyridine form which was spontaneously oxidized to the pyridine derivative 13. A similar mechanism was previously observed in the formation of pyridocoumarins starting from hydroxycoumarins and amine 1.17 At this stage, it seemed that this difference in reactivity was due to the methoxy substitution, since the introduction of a withdrawing group in this position (CF₃, entry 5) led to the desired spirane derivative. Further studies concerning this mechanism have been performed and will be reported elsewhere.

Finally, treatment of compound 9a with an excess of ethanethiol in the presence of BF₃·Et₂O gave in 92% yield the dithiolane derivative 15 which was converted into aminochroman derivative 16 by hydrogenolysis using W₂ Raney nickel in refluxing methanol (Scheme 6).

Alkylation of 16 with bromo derivative 17 (easily obtained from 3,3-tetramethyleneglutarimide and 1,4-
A New Efficient Synthesis of Spirocyclic Benzopyrans

Table 3  Reaction of Chromanones 8b–h with Amine 1

<table>
<thead>
<tr>
<th>Chromanones</th>
<th>Products</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>OMe</td>
<td>45</td>
</tr>
<tr>
<td>MeO</td>
<td>MeO</td>
<td>32</td>
</tr>
<tr>
<td>MeO</td>
<td>9d</td>
<td>41</td>
</tr>
<tr>
<td>OMe</td>
<td>9e</td>
<td>53</td>
</tr>
<tr>
<td>MeO</td>
<td>8g</td>
<td>45</td>
</tr>
<tr>
<td>OMe</td>
<td>9g</td>
<td>42</td>
</tr>
</tbody>
</table>

Scheme 5

Scheme 6
dibromobutane furnished 18 (demethoxy S 22178) in 81% yield.

In conclusion, the procedure described herein offers a simple and convenient process for the synthesis of the 3',4'-dihydrospiro[piperidine-2,3' (2'H)-benzopyran] framework, and substituted derivatives, from readily available materials. Synthetic efficiency was demonstrated through the synthesis of the demethoxy analogue of S 22178. Moreover, when methoxy substituents are present in the 5 or 8 positions, a new class of compounds (5- or 8-methoxy-4-methyl-10H-9-oxa-1-azaphenanthrenes) is accessible, and their use in natural product synthesis will be reported in due course.

All air- and moisture-sensitive reactions were carried out under an argon atmosphere. Anhyd solvents (Et₂O and THF) were freshly distilled from sodium–benzophenone under nitrogen prior to use. Petroleum ether refers to the fraction with bp 40–60 °C. ¹H and ¹³C NMR spectra were obtained with a Bruker instrument Advance DPX250 at 250.131 and 62.9 MHz, respectively. Chemical shifts (δ values) were reported in parts per million and coupling constants (J
values) in Hz. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. IR were recorded using NaCl film or KBr pellets on a Perkin–Elmer spectrometer FT PARAGON 1000PC. Mass spectra (MS) were recorded on a Perkin–Elmer mass spectrometer SCIEX API 300 by ion spray (IS). Mps were determined in open capillary tube and are uncorrected. Analytical TLC was performed on Merck 60F 254 silica gel precoated plates. Flash chromatography was performed using silica gel Merck 40–70 μm (230–400 mesh). Preparation of compounds 11a, 11b, 11c, 11d, 10e, 11f, 12a, 12b, 12c, 12d, 12e, 12f, 12g, 12h, 12i, and 8 have been previously described.

3-Cyanobenzopyrans 11; General Procedure
Under an argon atmosphere, salicylaldehyde (1 equiv) was dissolved in acrylonitrile (4.5 equiv) with DABCO (0.25 equiv). The mixture was refluxed for 18 h. The mixture was cooled to r.t. and aq NaOH (1 M) was added. The mixture was extracted with EtOAc, the organic layer was dried (MgSO₄), filtrated and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether–EtOAc, 9:1) to give the desired nitriles 11.

5-Nitro-2H-1-benzopyran-3-carboxylic Acid (12f)
Yield: 99%; beige solid; mp 211 °C.
IR (film): 1740 (C=O) cm⁻¹.
MS (IS): m/z = 220 (M⁻).

5-Trifluoromethyl-2H-1-benzopyran-3-carboxylic Acid (12g)
Yield: 87%; white solid; mp 186 °C.
IR (film): 3346–2734 (COOH), 1694 (C=O) cm⁻¹.
MS (IS): m/z = 230 (M⁻).

5-Trifluoromethyl-2H-1-benzopyran-3-carboxylic Acid (12h)
Yield: 99%; beige solid; mp 211 °C.
IR (film): 3346–2734 (COOH), 1694 (C=O) cm⁻¹.
MS (IS): m/z = 225 (M⁻).

3H-Naphtho[2,1-b]pyran-2-carboxylic Acid (12h)
Yield: 99%; beige solid; mp 211 °C.
IR (film): 3400–2502 (OH) cm⁻¹.

Ketones 8; General Procedure
Under an argon atmosphere, Et₃N (1.3 equiv) and diphenylphosphoryl azide (1.02 equiv) in anhyd toluene were added to a solution of acid 12 (1 equiv) in CH₂Cl₂. The mixture was warmed to 60 °C in order to distil CH₂Cl₂. To the mixture, toluene was added and the solution was refluxed and stirred for 1.5 h. The solution was cooled to r.t. and aq HCl (6 M) was added. The mixture was refluxed and stirred for 2 h, cooled to r.t. and extracted with CH₂Cl₂. The organic layers were dried (MgSO₄) and purified by flash chromatography (petroleum ether–EtOAc, 95:5) to give chromatone 8.

5-Trifluoromethyl-2H-1-benzopyran-3(4H)-one (8g)
Yield: 56%; yellow oil.
IR (film): 1740 (C=O) cm⁻¹.
MS (IS): m/z = 225 (M⁻).
Spirycyclic Derivatives 9; General Procedure
Under an argon atmosphere, chromanone 8 in anhyd CH₂Cl₂, TsOH (cat.), MgSO₄ (0.5 g) and amine 1 (1.1 equiv) were added. The solution was refluxed for 2 h. The solution was cooled to r.t. and 

BF₃·Et₂O (1.5 equiv) was added. The solution was refluxed for 18 h and the mixture was hydrolyzed with sat. aq NaHCO₃. The mixture was extracted with CH₂Cl₂, dried (MgSO₄), concentrated under reduced pressure and purified by flash chromatography (CH₂Cl₂–MeOH, 98:2) to furnish spirocyclic derivative 9.

3',4'-Dihydroxy[piperidine-(1,4-dioxo-8-azaspiro[4,5]decane)-2,3(2'H)-benzopyran] (9a)
Yield: 52%; colorless oil.

IR (film): 3686–3118 (NH) cm⁻¹.
Yield: 52%; colorless oil.

1H NMR (250 MHz, CDCl₃): δ = 1.67 (s, 2 H, 3-H), 1.73 (t, 2 H, J = 5.8 Hz, 5-H), 2.04 (br s, 1 H, NH), 2.79 (s, 2 H, 4'-H), 2.89–3.06 (m, 2 H, 6-H), 3.84 (d, 1 H, J = 11.0 Hz, 2'-H), 3.94 (s, 4 H, OCH₂CH₂O), 4.29 (d, 1 H, J = 11.0 Hz, 2'-H), 6.81–6.87 (m, 2 H, H₂Ar), 7.00–7.06 (m, 2 H, H₂Ar).

13C NMR (62.5 MHz, CHCl₃): δ = 35.3 (5-C), 37.9 (4'-C), 39.0 (5-C), 41.6 (3-C), 50.2 (2-C), 64.3 and 64.5 (OCH₂CH₂O), 70.4 (2'-C), 107.5 (2-C), 116.5 (CH₂Ar), 120.5 (C₁₀), 121.0 (CH₂Ar), 127.6 (CH₂Ar), 130.5 (CH₃Ar), 153.6 (8'-a-C).

MS (IS): m/z = 262 (M + 1).

Analytical data for C₈H₁₄NO₢: C, 69.23; H, 7.46; N, 5.53.

6-Methoxy-3',4'-dihydroxy[piperidine-(1,4-dioxo-8-azaspiro[4,5]decane)-2,3(2'H)-benzopyran] (9c)
Yield: 32%; yellow oil.

IR (film): 3690–3084 (NH) cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 1.67 (br s, 2 H, 3-H), 1.74 (t, 2 H, J = 5.9 Hz, 5-H), 2.79 (br s, 2 H, 4'-H), 2.93–3.08 (m, 2 H, 6-H), 3.73 (s, 3 H, OCH₃), 3.79 (d, 1 H, J = 11.0 Hz, 2'-H), 3.90–4.06 (m, 4 H, OCH₂CH₂O), 4.27 (d, 1 H, J = 11.0 Hz, 2'-H), 6.56 (d, 1 H, J = 2.7 Hz, 5'-H), 6.67 (dd, 1 H, J = 8.8, 2.7 Hz, 7'-H), 6.77 (d, 1 H, J = 8.8 Hz, 8'-H).

13C NMR (62.5 MHz, CHCl₃): δ = 35.3 (5-C), 38.1 (4'-C), 38.9 (6-C), 41.6 (3-C), 50.1 (2-C), 55.8 (OCH₃), 64.3 and 64.5 (OCH₂CH₂O), 70.5 (4'-C), 107.5 (4-C), 113.6 (CH₃Ar), 114.7 (CH₂Ar), 117.1 (CH₂Ar), 120.9 (C₁₀), 147.5 (C₁₀), 153.8 (C₁₀).

MS (IS): m/z = 292 (M + 1).

Analytical data for C₁₈H₂₁NO₄: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.51; H, 6.89; N, 4.72.

Pyridobenzopyran Derivatives 13 and 14; General Procedure
Following the same protocol described for the synthesis of spirocyclic derivatives 9, pyridine derivatives 13 and 14 were obtained starting from amine 1 and ketones 8b and 8e, respectively.

5-Methoxy-4-methyl-10H-9-oxa-1-azepanethrene (13e)
Yield: 45%; brown oil.

IR (film): 1277 (CO) cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 2.29 (s, 3 H, ArCH₃), 3.89 (s, 3 H, OCH₃), 4.91 (s, 2 H, 10-H), 6.59 (d, 1 H, J = 8.1 Hz, H₂α), 6.71 (d, 1 H, J = 8.1 Hz, H₂β), 6.78 (d, 1 H, J = 5.1 Hz, H₂γ), 7.23 (t, 1 H, J = 8.1 Hz, 6-H), 8.19 (d, 1 H, J = 5.1 Hz, H₂β).

13C NMR (62.5 MHz, CHCl₃): δ = 22.0 (ArCH₃), 55.2 (OCH₃), 71.9 (10-C), 105.2 (CH₁₀), 112.3 (C₁₀), 124.2 (C₁₀), 126.0 (CH₁₀), 130.1 (CH₁₀), 145.0 (C₁₀), 146.4 (C₁₀), 154.8 (C₁₀), 156.8 (C₁₀), 158.3 (C₁₀).

MS (IS): m/z = 228 (M + 1).

Analytical data for C₁₈H₁₄NO₄: C, 73.99; H, 5.77; N, 6.17. Found: C, 74.12; H, 5.68; N, 6.29.
**8-Methoxy-4-methyl-10H-9-oxa-1-azaphenanthrene (14)**

Yield: 53%, brown oil.

IR (film): 1235 (COC) cm\(^{-1}\).

\({ }^{1} \text{H NMR} (250 \text{ MHz, CDCl}_3): \delta = 2.62 (s, 3 \text{ H, ArCH}_2), 3.93 (s, 3 \text{ H, OCH}_2), 5.16 (s, 2 \text{ H, 10-H}), 6.92 (dd, 1 \text{ H, J = 8.1, 1.2 Hz, 6-H or 8-H}), 7.05 (t, 1 \text{ H, J = 8.1 Hz, 7-H}), 7.12 (d, 1 \text{ H, J = 5.0 Hz, 2-H or 3-H}), 7.33 (dd, 1 \text{ H, J = 8.1, 1.2 Hz, H}_{\text{pyr}}), 8.29 (d, 1 \text{ H, J = 5.0 Hz, H}_{\text{pyr}}).\)

\({ }^{13} \text{C NMR} (62.5 \text{ MHz, CDCl}_3): \delta = 22.5 (\text{ArCH}_2), 56.2 (\text{OCH}_2), 71.2 (10-C), 121.2 (\text{CH}_{\text{Ar}}), 121.5 (\text{CH}_{\text{Ar}}), 123.5 (\text{C}_{\text{Ar}}), 125.4 (\text{C}_{\text{Ar}}), 127.0 (\text{CH}_{\text{Ar}}), 129.8 (\text{C}_{\text{Ar}}), 147.2 (\text{CH}_{\text{Ar}}), 149.3 \text{ and } 153.6 (5-C, 8a-C).\)

MS (IS): \(m/z = 228 (M + 1).\)

**3,4-Dihydropyrophenine[1,4-dithia-8-azaspiro[4.5]deca-2,3(2H)-benzopyran] (15)**

Under an argon atmosphere, ethanedithiol (0.18 mL, 1.91 mmol) was added to acetal 9a (0.1 g, 0.38 mmol) in CH\(_2\)Cl\(_2\) (5 mL). The mixture was refluxed and stirred for 24 h. The solution was cooled to r.t., hydrolyzed, and extracted with CH\(_2\)Cl\(_2\). The organic layers were dried (MgSO\(_4\)) and concentrated under reduced pressure. The crude was purified by flash chromatography (CH\(_2\)Cl\(_2\)–MeOH, 98:2) to give dihydroetioacetal 15.

Yield: 0.103 g (92%); yellow solid.

IR (film): 3317 (NH) cm\(^{-1}\).

Analytical Calcd for C\(_{14}\)H\(_{13}\)NO\(_2\): C, 73.99; H, 5.77; N, 6.17. Found: C, 73.89; H, 5.89; N, 6.45.

**3,4-Dihydropyrophenine[1,4-dithia-8-azaspiro[4.5]decane]-2,3(2H)-benzopyran] (16)**

Under an argon atmosphere, to a solution of dithioacetal 0.34 mmol) in EtOH (5 mL), Raney nickel W\(_2\) (0.34 g) (washed with EtOH) was added to acetal 15. The mixture was refluxed and stirred for 2 h and cooled to r.t. The mixture was filtered through a Celite® filter, washed with EtOH (2 mL), and dried. The product was dissolved in aq NaOH (1 M; 5 mL) and extracted with CH\(_2\)Cl\(_2\). The organic layers were dried (MgSO\(_4\)) and concentrated under reduced pressure. The mixture was reflushed for 18 h. After total consumption of starting material, the mixture was hydrolyzed and the crude product was extracted with CH\(_2\)Cl\(_2\) and dried (MgSO\(_4\)). After column chromatography (CH\(_2\)Cl\(_2\)–MeOH, 95:5), 16 was obtained.

Yield: 0.07 g (72%); colorless oil.

IR (film): 1727 and 1682 (C=O) cm\(^{-1}\).

Analytical Calcd for C\(_{26}\)H\(_{36}\)N\(_2\)O\(_3\): C, 73.55; H, 8.55; N, 6.60. Found: C, 73.89; H, 8.73, N, 6.45.

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